from "Experimental Tobacco Carcinogenesis," 11/22/68

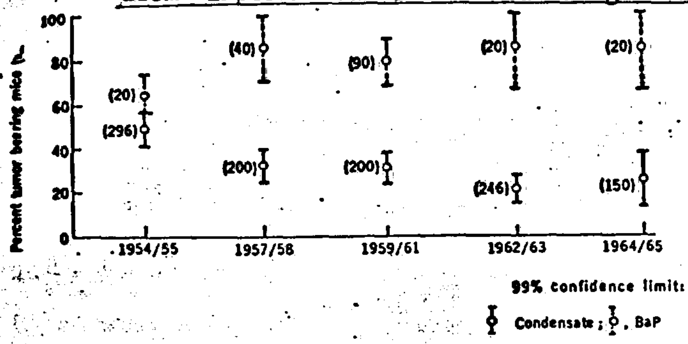

Fig. 5. Decline of tumorigenicity, on mouse skin, of cigarette smoke condensates as tested during the period 1954–65 compared with the response to a 0.005-percent benzo[*a*]pyrene solution. Numbers in parentheses are numbers of mice per group.

or cocarcinogenic, smoke constituents as the indicators mentioned above. For one thing, *N*-nitrosamines, nitroolefins, and groups such as aromatic amines have specific precursors for individual compounds. Furthermore, it is necessary to consider the complexity of biologic responses to structurally similar coexistent compounds.

Reduction of Tumorigenicity

One major objective of experimental tobacco carcinogenesis is the reduction of the tumorigenicity of cigarette smoke and other tobacco products. As we have stated, it is possible, on the basis of chemical indicators, to predict a given biologic activity, and in general we have found a meaningful correlation between such indicators and biologic findings.

Among feasible methods for reducing the tumorigenic and ciliatoxic properties of cigarette smoke are modification of breeding, culturing, and curing of tobacco and selection of tobacco according to its chemical composition (for example, high nitrate content, low nicotine content). The use of additives, choice of optimum tobacco cut and paper of optimum porosity, the use of stems, and the addition to cigarette tobaccos of shredded "reconstituted tobacco sheet" (a material prepared from tobacco dust and fines combined with adhesives) are other measures effective in reducing the yield of particulate matter in the smoke and/or diminishing the tumorigenicity of the smoke condensate.

Mechanical and selective smoke filtration is effective in reducing the yield of particulate matter from the smoke, and selective filtration can suppress the ciliatoxicity of the smoke.

Nonselective reduction. Various studies have established a dose response for the tumorigenicity of tobacco "tar" (*5, 52*). Thus reduction of the "tar" and nicotine yield through modification of agricultural practices, selection of "low-tar-yielding" tobaccos, use of reconstituted tobacco, and effective mechanical filtration of the aerosol particles diminishes exposure to "tar" and nicotine and thus benefits the smoker, provided he does not smoke more cigarettes.

Some of these measures have been applied in increasing degrees during the past 15 years, with the result that "tar" and nicotine yields in the smoke of domestic cigarettes have been gradually lowered.

Selective reduction. Most stimulating to academic research are attempts to selectively reduce the carcinogenicity and ciliatoxicity of tobacco smoke. Since the formation of initiating carcinogens in tobacco smoke is probably a result of the degree of combustion and possibly of the presence of certain specific precursors, a modification of either of these factors may lead to a reduction in the concentration of initiating carcinogens.

In recent years the choice of "low-tar-yield" tobaccos may have contributed to the selective reduction of the carcinogenicity of "tars." Several studies demonstrated that cigarettes of comparable weight deliver significantly varying amounts of "tar" when they differ significantly in the degree of combustion, as indicated by the number of puffs required to reach a given butt length. We might therefore expect that cigarettes made of "low-tar-yield" tobaccos would show a selective reduction of those substances that are specifically a consequence of incomplete combustion. Benzo[*a*]pyrene is such a substance, and we find that the significant reduction in the particulate matter and the tumorigenic activity of the condensate of smoke from American cigarettes has been paralleled by a reduction in benzo[*a*]pyrene concentration over the past 15 years (the average benzo[*a*]pyrene content of 1 gram of "tar" changed from 1.2 micrograms to 0.9 microgram). Thus, a general modification of the composition of American cigarettes has led to a reduction not only in the overall "tar" yield but apparently also in carcinogenic activity (Fig. 5).

The type of polynuclear aromatic hydrocarbon pyrosynthesized is determined by the temperature profile of the burning tobacco. Modification of this determinant, however, is difficult (*5*). Comprehensive studies made in our laboratory have shown that adding nitrates (especially alkali nitrates), at a concentration of 5 to 8 percent, to tobacco or selecting nitrate-rich tobaccos will significantly reduce the yield of polynuclear aromatic hydrocarbons and the tumorigenic activity of the resulting "tars" (*17*) (Fig. 3). Since most such hydrocarbons in smoke are synthesized from the pyrolytically formed radicals consisting of carbon and hydrogen, we considered the possibility that nitrogen oxides (originating from alkali nitrates) may react in the hot zones with these radicals and thus inhibit the pyrosynthesis of polynuclear hydrocarbons. This hypothesis is supported by the identification of nitroalkanes in tobacco smoke and the dependence of their concentrations on the nitrate content of the tobacco (Fig. 6).

The addition of nitrates does not, however, significantly affect the tumor-promoting activity of a given tobacco "tar"—a finding that underscores the differences in the formation of tumor initiators and promoters in cigarette smoke.

Perhaps, owing to the presence of precursors, flue-cured and sun-cured tobaccos tend to yield more benzo[*a*]pyrene and more phenols in the smoke than air-cured tobaccos and also tend to produce "tars" that yield more tumors in the mouse-skin assay (*5*). Qualitative differences in the types of tobacco and differences in the enzymatic processes that occur during the curing of these tobaccos obviously influence smoke constituents. For one thing, flue-